REMARKS

The Drawings

Applicants thank the Examiner for accepting the drawings submitted on December 26, 2001.

The Claim Amendments

Applicants have amended claim 85 to recite a "whole" antibody and to delete the term "about." These amendments are supported throughout the specification as filed. *See, e.g.*, page 12, line 30 - page 14, line 19; page 41, lines 21-27; page 42, lines 5-19.

Applicants have also amended claim 86 (and claims 87-90 that depend from claim 86), claim 91 that refers to claim 86 (and newly added claims 92-93) and added claims 92-93 to recite the total volume of each of the micro-batch crystallizations. Support for these amendments is found, for example, in Example 36 (total volume 33 µl); Example 37 (total volume 75 µl) and Examples 4, 5, and 32 (total volume 110 µl).

Finally, applicants have added claim 94. It recites Infliximab crystals produced by the methods of any of claims 86-89, and 92-93. Claim 94 is supported, for example, in Examples 34, 36 and 37.

The Rejections

1. The Previous Rejections

Applicants thank the Examiner for her consideration of their February 13, 2006 arguments and her withdrawal of all of the previous rejections.

2. The New Rejections

(a) 35 U.S.C. § 112, second paragraph

(i) Claims 86-91 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being incomplete for omitting essential steps from the claimed method. In particular, the Examiner argues that the relation of step (c) to step (d) is unclear. Applicants traverse.

Step (c) of claims 86-91 (and new claims 92-93) recites selecting from a series of different micro-batch crystallization solutions (buffer and antibody) one solution that produces antibody crystals of good quality and yield. Step (d) of those claims then recites using the crystallization buffer that characterizes the selected solution in a large batch crystallization of the antibody. The claim does not require seeding the large batch crystallization with a crystal from step (c) or using the protein concentration of Step (c). What it requires is that the crystallization buffer of the crystallization solution selected in Step (c) be used in Step (d). That instruction is clear and definite.

Applicants request that the Examiner reconsiders and withdraw this rejection.

(ii) Claim 85 stands rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite in the context of the term "about" 20 mg/ml. Applicants have amended the claim to delete "about." This clarifies the claim but does not limit or narrow it.

(b) 35 U.S.C. § 112, first paragraph: Enablement

(i) Claims 84 and 85 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. In particular, the Examiner argues that the claimed crystals of Infliximab are not enabled except as produced by the specific methods recited in the specification, i.e., Examples 34-37. Applicants traverse.

Claims 84 and 85 are product claims. Claim 84 recites a crystal of Infliximab. Claim 85 recites a pharmaceutical composition comprising an antibody crystal.

Product claims are enabled by teaching one way of making the product. For example, a chemical compound is enabled if the specification teaches one way of making it. For this reason alone, claims 84 and 85 are enabled.

Here, however, there is also a second reason why these claims are enabled. Examples 34-37 provide four specific crystallizations of Infliximab.

Example 34

100 mg Infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg. monobasic sodium phosphate, 6.1 mg dibasic sodium phosphate in 2 ml of sterile water.

50 mg of antibody (50 mg/ml) mixed with 35% ethoxyethanol, 0.2 M lithium sulfate, 0.1 M Tris, pH 8.6

Tumbling at room temperature at 50 rpm. Overnight incubation.

Example 35

Infliximab (as in Example 34) in 40% (w/v) PEG 400, 0.1 Tris buffer, 200 mM lithium sulfate, pH 8.5

Tumbling and incubation as in Example 34.

Example 36

25 µl Infliximab (50 mg/ml in 0.1 M Tris HCl buffer, pH 7.0), 3 µl 1 M calcium chloride, and 5 µl 100% polyethylene glycol monomethyl ether 550 (PEG MME 550)

Incubation (without agitation) overnight at room temperature

Example 37

25 µl Infliximab (20 mg/ml water) in 50 µl crystallization buffer (20% PEG 300, 0.1 M, Tris pH 8.5, 5% PEG 8000 and 10% glycerol)

Incubate (without agitation) overnight at room temperature.

Therefore, the specification not only provides one way of making the claimed Infliximab crystals it provides four very different ways. Each way produced crystals. Each uses 20 mg/ml of Infliximab or more. Such teachings support claim 84 (and new claim 94). They also support claim 85. Indeed, the other specific examples – which are directed to other antibodies and other crystallization conditions, also support claim 85. Applicants request that the Examiner reconsider and withdraw this rejection.

(ii) Claims 86-91 stand rejected under 35 USC § 112, first paragraph, because the crystalizations, while enabling the large-batch production of Retuximab and

Trastuzumab, allegedly does not enable the production of any other antibody. Applicants traverse.

As the Examiner has acknowledged, the specification teaches and enables the large-batch crystallization of Retuximab and Trastuzumab. Indeed, the specification provides specific examples of crystallizations of these antibodies under various conditions. The specification, however, goes much further. It also teaches that the process described for these specific antibodies is directly applicable to nine other specific antibodies – infliximab, abciximab, palivizumab, murumomab, gemtuzumab, ozogamicin, basiliximab, daclizumab, etanercept and ibritumomab. *See, e.g.*, 38. All of these antibodies are different. Thus, these specific examples and the specific teaching that the processes of those examples are also useful for the large batch crystallization of the nine other antibodies (in fact any antibody) provides far more than the enablement required for claims 86-91.

Given this teaching, the Examiner needs to do more than just argue that crystallization is unpredictable. Applicants have overcome that concern by demonstrating that conditions selected in the microcrystallizations of this invention are useful in the claimed large batch crystallizations for a diverse set of antibodies. As the Examiner has argued, the "conversion of microliter-size crystallization trials into industrial dimensions, however, may be a challenging task." Applicants have solved that challenge. Applicants have discovered and taught a systematic process to produce successful large batch conversions. This process is characterized by screening buffer solutions in volumes much larger than those used in the

traditional microliter-size crystallization trials. Applicants' invention takes the large batch crystallization process away from the random trial-and-error process. Applicants request that the Examiner reconsider and withdraw this rejection.

(iii) Claims 90-91 stand rejected under 35 USC § 112, first paragraph, as allegedly not being enabled for the production of Infliximab crystals by a large batch crystallization process. Applicants traverse.

The specification teaches and claim 90 recites a process wherein microbatch crystallization buffers that result in antibody crystals of good quality and yield are selected and used successfully in the large-bath crystallization of that antibody. Claims 91 and 94 recite antibodies made using those processes. Example 34 - 37 provide four different microbatch crystallization buffers specific for Infliximab. Each results in Infliximab crystals of good quality and yield. Thus, following the teachings of the specification any of those conditions are useful in the large batch crystallization of Infliximab. Indeed, applicants have produced large batches of Infliximab crystals using those diverse methods

The Examiner has pointed to no reason, and there is none, why these buffers would not produce Infliximab crystals in a large batch crystallization. Applicants request that the Examiner reconsider and withdraw this objection.

(c) 35 USC § 112, first paragraph: Written Description

Claims 84-85 stand rejected under 35 USC § 112, first paragraph, for allegedly being broader than the written description of the specification. Specifically, the Examiner argues that "while the structure and function of some species of [the claimed] genera of Infliximab crystals are disclosed in the specification, the common characteristics of the species that define said genera are not disclosed". Applicants traverse.*

As applicants have already demonstrated in the context of the § 112 alleged lack of enablement of claims 84-85, the specification provides substantial and diverse written description of Infliximab and other antibody crystals. First, the specification describes that its process of selecting an appropriate crystallization buffer in a microcrystallization and using that buffer in a large batch crystallization is generally applicable to all antibodies. Second, the specification has several actual examples of using that process to produces diverse antibody crystals in large batch crystallizations. Thus, applicants have provided the necessary written description of the claimed antibodies.

Prior to applicants' invention, large batch crystallization of antibodies was virtually impossible. The challenge lay in the non-transferability of crystallization conditions to a large scale from trial volumes of, for example, 1-2 µl, 5 µl, 3-10 µl, 10 µl, 2-10 µl (*see, e.g.*, Jan Drenth, Principles of Protein X-Ray Crystallography, Second Edition, pages 4, 5, 10,

* Applicants have amended claim 85 to recite "whole" antibodies.

and 15). Applicants, however, have described and taught in this application a method to successfully produce large batches of antibody crystals by screening buffer solutions in volumes much larger than those used in the traditional microliter-size crystallization trials. Applicants' method has taken the large batch crystallization process away from the random trial-and-error process.

The large-batch crystallization method described in this application is not for producing crystals for X-ray structural analysis. Thus, although structural analysis requires one to produce one single, large, appropriately shaped crystal for X-ray diffraction, applicants here teach methods of producing large quantities of uniform crystals within a short period of time that have smaller sizes and consistent yields. The criteria and experimental demands applicable to crystals of X-ray qualities simply do not transfer directly to crystals of industrial qualities. Applicants have successfully used the method disclosed to produce antibodies in large batches, which has not been done by others.

In terms of "common features", the specification also provides the necessary description. The feature is antibody crystals. Furthermore, the specification provides the necessary generic/specific written description of a process of making those crystals: select the appropriate buffer in a microcrystallization and use the selected buffer in a large batch crystallization.

Applicants request that the Examiner reconsider and withdraw this rejection.

(d) 35 USC § 102(b)—Anticipation

Claim 85 stands rejected under 35 USC § 102(b) as allegedly anticipated by Cheetham et al., JMB 284: 85-99 (1998) ("Cheetham"). Applicants traverse.

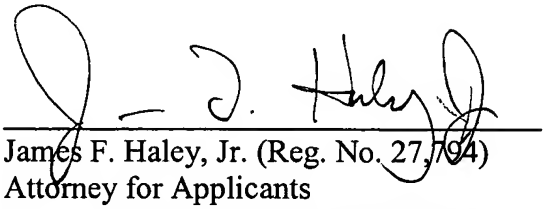
The Examiner argues that Cheetham teaches the crystallization of rat anti CD52 in a buffer at 20 mg/ml. She, then, concludes that the antibody crystal in the mother liquor of Cheetham anticipates claim 85. Cheetham does not anticipate amended claim 85. That claim recites "whole" antibodies. Cheetham teaches only the crystallization of an antibody fragment, not a whole antibody, which is larger than a fragment and more difficult to crystallize. Thus, claim 85 as amended is not anticipated by Cheetham.

Applicants request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Applicants request reconsideration of this application and the pending claims in view of the foregoing remarks. Early allowance of the pending claims is requested.

Respectfully submitted,



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